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Vitamin D for the management of asthma (Protocol)

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[Intervention Protocol]

Vitamin D for the management of asthma

Adrian Martineau[1], Andrea Takeda[2], Ulugbek Nurmatov[3], Aziz Sheikh[4], Chris J Griffiths[5]

[1]Barts and the London School of Medicine, Queen Mary University of London, London, UK. [2]Queen Mary University of London, Barts & The London School of Medicine, Research Design Service, Centre for Primary Care and Public Health, Blizard Institute, London, UK. [3]Allergy & Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK. [4]Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK. [5]Centre for Primary Care and Public Health, Blizard Institute, Barts and the London Medical School, London, UK

Contact address: Adrian Martineau, Barts and the London School of Medicine, Queen Mary University of London, London, UK. a.martineau@qmul.ac.uk.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the efficacy of administration of vitamin D and its hydroxylated metabolites in reducing asthma exacerbations and improving asthma symptom control.

BACKGROUND

Description of the condition

Asthma is a chronic inflammatory condition of the airways, characterised by recurrent attacks of breathlessness, wheezing, cough and chest tightness, termed 'exacerbations'. The prevalence of asthma varies widely between countries. In children, the prevalence of severe asthma symptoms ranges from 0% (India) to 20.3% (Costa Rica) (Lai 2009); in adults, the prevalence of doctor-diagnosed asthma ranges from 0.2% (China) to 21.0% (Australia) (To 2012). Exacerbations represent the major cause of morbidity and mortality in patients with asthma (Johnston 2006). Asthma exacerbations are classified as severe when they result in hospitalisation or death, and moderate when they prompt a need for a change in treatment, such as initiation of systemic corticosteroids, without causing death or hospitalisation (Reddel 2009). Common precipitants of asthma exacerbation include acute respiratory infections and exposure to allergens and particulates (Singh 2006).

Description of the intervention

Vitamin D is a pre-pro-hormone that has two parent forms: cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Cholecalciferol is synthesised in human skin from its precursor molecule 7-dehydrocholesterol on exposure to ultraviolet B (UVB) radiation in sunlight; it may also be ingested, either in the diet (primarily from eating oily fish) or in vitamin D supplements. Ergocalciferol is the plant and fungal form of the vitamin, which may occasionally be ingested in the diet (primarily by eating fungi) or in vitamin D supplements. In situations where cutaneous exposure to UVB radiation of appropriate intensity is limited (e.g. during winter at latitudes above 34ºN or below 34ºS, or in settings where people do not regularly expose their skin to sunlight), dietary sources of

vitamin D and/or vitamin D supplements may be required to meet the body's vitamin D requirement (Holick 2007).

Following cutaneous synthesis or ingestion, both forms of parent vitamin D undergo metabolism to form 25-hydroxyvitamin D (25(OH)D), the major circulating vitamin D metabolite whose serum concentration indicates vitamin D status. 25-hydroxylation may occur in the liver and in extra-hepatic tissues, including leucocytes (Holick 2007). Serum 25(OH)D concentrations < 50 nmol/L are widely accepted to indicate vitamin D deficiency; concentrations < 25 nmol/L represent profound deficiency. Concentrations of 50-74 nmol/L may represent a milder state of inadequate vitamin D status, commonly termed 'vitamin D insufficiency'. 25(OH)D undergoes a second hydroxylation step at the 1-alpha position to form the active vitamin D metabolite 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) - the steroid hormone and active vitamin D metabolite which mediates the biological actions of vitamin D by binding the vitamin D receptor to regulate gene expression (Holick 2007). This 1-alpha hydroxylation step is catalysed by the enzyme CYP27B1, which is expressed in multiple tissues including the kidney, leucocytes and pulmonary epithelium; expression of CYP27B1 in leucocytes and pulmonary epithelium is up-regulated in response to infection and inflammation.

This review will include studies which evaluate the effects of administration, by any route and at any dose, of vitamin D_3, vitamin D_2, 25(OH)D or $1,25(OH)_2D$. Vitamin D_3, vitamin D_2 and 25(OH)D are usually administered orally; the 'parent compounds' vitamin D_3 and vitamin D_2 may also be given intramuscularly. Intramuscular administration of a bolus dose of vitamin D induces a slower increase and a lower peak in serum 25(OH)D than oral administration of the same dose (Romagnoli 2008), and consequently this route of administration is not widely employed in clinical trials of vitamin D supplementation. The functional in vivo half-life of 25(OH)D in the circulation is 1 to 2 months; accordingly, it takes at least 3 months to attain steady-state concentrations of 25(OH)D in response to daily administration of vitamin D (Heaney 2003). Because of the relatively long half-life of 25(OH)D, parent vitamin D and 25(OH)D may be administered intermittently as well as daily: weekly and monthly dosing regimens are often employed, and more widely spaced dosing regimens are also used. However, dosing less frequently than two monthly results in large non-physiological fluctuations in serum 25(OH)D concentration, which may cause undesirable effects (Vieth 2009; Martineau 2012; Hollis 2013). The influence of dosing interval on biological responses to administration of vitamin D is an area of active research in the field.

How the intervention might work

About 1 billion people worldwide are estimated to have 25(OH)D levels < 75 nmol/L (Holick 2007). Inadequate vitamin D status has been reported to be common among asthma patients in a variety of settings, and several studies have demonstrated independent associations between inadequate vitamin D status and increased risk of exacerbations (Brehm 2010; Brehm 2012; Confino-Cohen 2014). Administration of vitamin D_3, vitamin D_2 or 25(OH)D results in increasing circulating concentrations of 25(OH)D. This 25(OH)D acts as a substrate for CYP27B1 expressed in the kidney and multiple extra-renal tissues. Of particular relevance for asthma, CYP27B1 expression in the airway and leucocytes is induced during infection and inflammation, so that the active vitamin D metabolite $1,25(OH)_2D$ is synthesised locally in the lung. $1,25(OH)_2D$ ligates the vitamin D receptor (VDR) to induce antimicrobial activity (e.g. by induction of antimicrobial peptide expression) and exert anti-inflammatory activity (e.g. by induction of the anti-inflammatory cytokine IL-10, suppression of pro-inflammatory TNF and IFN-γ- inducible chemokines and inhibition of LPS-induced synthesis of reactive oxygen species) (Lan 2014; Mann 2014). This combination of antimicrobial, antiviral and anti-inflammatory activity might decrease the risk of exacerbations, which are often precipitated by respiratory infection, and which are characterised by dysregulated pulmonary inflammation. Of particular relevance to asthma, $1,25(OH)_2D$ has been shown to enhance responsiveness to inhaled corticosteroids (ICS) for production of interleukin-10 (Xystrakis 2006). This finding raises the possibility that administration of vitamin D or 25(OH)D may therefore have a role in reducing exacerbation risk and improving symptom control in combination with ICS, as well as independently. There is controversy, however, regarding what serum 25(OH)D concentration, if any, is optimum for reducing the risk of asthma exacerbation.

Why it is important to do this review

There is considerable interest in the potential of administration of vitamin D to reduce exacerbation risk and improve asthma symptom control. Two small trials of vitamin D supplementation in children with asthma treated with inhaled corticosteroids have reported reduced rates of exacerbation among participants randomised to the intervention arm (Majak 2011; Yadav 2014), and one small trial showed no effect of vitamin D supplementation on inflammatory markers or lung function (Bar Yoseph 2014). One larger trial in adults has also reported a trend towards reduced exacerbation rate in the intervention arm (adjusted Hazard Ratio 0.63, 95% confidence interval (CI) 0.39 to 1.01) (Castro 2014). Other trials are either in progress or completed but as yet unpublished. Meta-analysis of these trials has the potential to increase statistical power to detect effects of administering vitamin D on exacerbation risk and symptom control both in study populations as a whole, and within subgroups who might be expected to derive particular benefit from this intervention (e.g. those with lower vitamin D status at enrolment).

OBJECTIVES

To evaluate the efficacy of administration of vitamin D and its hydroxylated metabolites in reducing asthma exacerbations and improving asthma symptom control.

METHODS

Criteria for considering studies for this review

Types of studies

We will review double-blind randomised placebo-controlled trials of at least twelve weeks' duration. We will include studies reported as full-text and unpublished data. Studies published as abstract only will also be included, but we will note that they are pending definitive evaluation as and when fuller reports are available.

Types of participants

We will include children and adults with a clinical diagnosis of asthma, based on the presence of characteristic symptoms and variable airflow obstruction. No restrictions regarding disease severity, baseline vitamin D status or duration of treatment with asthma medication will be imposed, in order to maximise generalisability.

Types of interventions

We will include studies in which vitamin D_3, vitamin D_2, 25(OH)D or $1,25(OH)_2D$ are administered at any dose.

Types of outcome measures

Primary outcomes

The primary outcome of this review is asthma exacerbation treated with systemic corticosteroids.

Secondary outcomes

Effectiveness

1. Asthma exacerbation requiring hospital admission;
2. Asthma exacerbation precipitating an emergency department visit;
3. Fatal asthma exacerbations;
4. Symptom control as judged by use of a validated instrument;
5. Time off school or work;
6. $Beta_2$agonist use;
7. Asthma quality of life as judged by use of a validated instrument.

Physiological/biochemical

1. Peak expiratory flow monitoring;
2. Spirometric values (forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC));
3. Biomarkers of asthma control (exhaled nitric oxide, lower airway eosinophilia in induced sputum or bronchoalveolar lavage, other immunological parameters);
4. Airway reactivity.

Health economic

1. Costs from the perspective of healthcare providers.

Safety

1. Proportion of patients experiencing an adverse event attributed to administration of vitamin D or its metabolites;
2. Proportion of patients experiencing any severe adverse event, irrespective of causation;
3. Proportion of patients withdrawing from the trial.

Search methods for identification of studies

Electronic searches

We will identify trials from the Cochrane Airways Group's Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We will search all records in the CAGR using the search strategy in Appendix 2. We will also conduct searches of ClinicalTrials.gov (www.ClinicalTrials.gov), the WHO trials portal (www.who.int/ictrp/en/), the ISRCTN clinical trials register (http://www.controlled-trials.com/isrctn/), the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/) and the UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for trial information.

We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

We will contact a panel of international experts for additional references and information on trials in progress.

Data collection and analysis

Selection of studies

Two review authors (ARM, AT) will independently screen for inclusion the titles and abstracts of all the potentially relevant studies we identify as a result of the search, and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication and two review authors (ARM, AT) will independently screen the full-text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third person (CJG or AS). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data, which has been piloted on at least one study in the review. Two review authors (ARM, AT) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, body mass index, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (ARM, AT) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (CJG or AS). One review author (AT) will transfer data into the RevMan 2014 file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (ARM) will spot-check study characteristics for accuracy against the trial reports.

Assessment of risk of bias in included studies

Two review authors (TBA, AT) will independently assess the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (CJG or AS). We will assess the risk of bias according to the following domains.

1. Random sequence generation;
2. Allocation concealment;
3. Blinding of participants and personnel;
4. Blinding of outcome assessment;
5. Incomplete outcome data;
6. Selective outcome reporting;
7. Other biases, including study size

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios, since the rate of exacerbations may vary widely between studies, and the weights for each study using relative risk will be heavily dependent on the choice of outcome measure. We will analyse continuous data as

mean difference or standardised mean difference. We will enter data presented as a scale with a consistent direction of effect.
We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.
We will narratively describe skewed data reported as medians and interquartile ranges.
Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.
For outcomes measured at different time points, we will include the longest time point after randomisation.

Unit of analysis issues

Where data are expressed in unconventional units of analysis we will convert them to conventional units, liaising with authors if required.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis**.**

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity (I^2 > 40%) we will report it and explore possible causes by pre-specified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases.

Data synthesis

We expect significant heterogeneity: accordingly, we will use a random-effects model and perform a sensitivity analysis with a fixed-effect model.
An intention-to-treat model will be used to analyse data when possible. Continuous data will be analysed as a mean difference; dichotomous data will be reported as odds ratios. Number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) for adverse events will be calculated where appropriate, to give an indication for each dichotomous outcome, to reflect the number of patients required to achieve a benefit or disbenefit with the intervention.
Means and standard deviations (SDs) will be used when available. We will approach authors where data are not reported. Values will be extracted from graphs if authors do not respond.

'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: incidence of moderate/severe asthma exacerbation; proportion of patients with one or more emergency department attendance or hospitalisation for asthma; asthma symptom control; asthma quality of life; lung function; biomarkers of asthma control; and incidence of severe adverse events attributed to administration of vitamin D. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the pre-specified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software.
We will calculate NNTB from the control group event rate (unless the population event rate is known) and odds ratios using the Visual Rx NNT calculator (http://www.nntonline.net/visualrx/).
We will list trials in progress.
We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Baseline vitamin D status (e.g. serum 25(OH)D < 50 nmol/L vs. ≥ 50 nmol/L). If data on baseline vitamin D status are unavailable, we will investigate whether the effects of administering vitamin D vary according to proxy measures of vitamin D status (e.g. season of randomisation, latitude of residence);
2. Age (e.g. children aged < 5 years versus 5 to 16 years versus adults);
3. Severity of asthma and concomitant asthma treatment being taken (e.g. taking versus not taking ICS, taking versus not taking leukotriene receptor antagonists);
4. The dose (e.g. daily equivalent of < 400 IU versus 400 to 2000 IU versus > 2000 IU) and form of vitamin D administered (e.g. cholecalciferol versus calcitriol);
5. The frequency of administration (e.g. daily versus intermittent bolus doses);
6. Genetic variation in pathways of vitamin D metabolism, transport and signalling (e.g. GC 2/2 versus 2/1 versus 1/1

genotype for the Gc polymorphism of the vitamin D binding protein);

7. Body mass index (e.g. < 25 kg/m^{2}versus ≥ 25 kg/m^2).

We will use the following outcome in subgroup analyses.

1. Severe asthma exacerbation.

We will use the formal test for subgroup interactions in RevMan 2014 .

Sensitivity analysis

We plan to carry out the following sensitivity analysis:

1. Exclusion of publications at high risk of bias in one or more of the following domains: sequence generation, allocation concealment, blinding, completeness of outcome data or selective outcome reporting.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*T he Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly

(*Continued*)

CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.

16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to retrieve trials from the CAGR

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Vitamin D Explode All
#6 MeSH DESCRIPTOR Vitamin D Deficiency Explode All
#7 "vitamin d"
#8 #5 or #6 or #7
#9 #4 and #8

(in search line #1, MISC1 refers to the field in the record where the reference has been coded for condition, in this case, asthma)

CONTRIBUTIONS OF AUTHORS

CJG and AM wrote the protocol. AS, UN and AT commented on it.

DECLARATIONS OF INTEREST

No conflicts of interest to declare.

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Internal sources

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Chris Griffiths

External sources

- No sources of support supplied